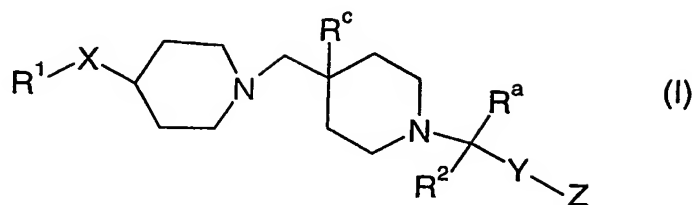


CLAIMS

1. A compound of formula (I):



wherein:

X is CH<sub>2</sub>, C(O), O, S, S(O), S(O)<sub>2</sub> or NR<sup>3</sup>;

Y is a bond, C<sub>1-6</sub> alkylene (optionally substituted by C<sub>1-4</sub> alkyl or phenyl), phenylene (optionally substituted by halogen, hydroxy, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy) or heterocyclylene (optionally substituted by halogen, hydroxy, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy);

Z is CO<sub>2</sub>R<sup>b</sup>, NHS(O)<sub>2</sub>CF<sub>3</sub>, S(O)<sub>2</sub>OH, OCH<sub>2</sub>CO<sub>2</sub>R<sup>b</sup> or tetrazolyl;

R<sup>1</sup> is hydrogen, C<sub>1-6</sub> alkyl, aryl or heterocyclyl;

R<sup>2</sup> is hydrogen, C<sub>1-6</sub> alkyl, aryl or heterocyclyl;

R<sup>a</sup> and R<sup>b</sup> are, independently, hydrogen or C<sub>1-4</sub> alkyl; or when R<sup>2</sup> is aryl or heterocyclyl R<sup>a</sup> may be C<sub>2-3</sub> alkylene forming a ring with an ortho position on R<sup>2</sup>; R<sup>c</sup> is hydrogen or hydroxy;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, cyano, nitro, hydroxy, oxo, S(O)<sub>p</sub>R<sup>4</sup>,

OC(O)NR<sup>5</sup>R<sup>6</sup>, NR<sup>7</sup>R<sup>8</sup>, NR<sup>9</sup>C(O)R<sup>10</sup>, NR<sup>11</sup>C(O)NR<sup>12</sup>R<sup>13</sup>, S(O)<sub>2</sub>NR<sup>14</sup>R<sup>15</sup>,

NR<sup>16</sup>S(O)<sub>2</sub>R<sup>17</sup>, C(O)NR<sup>18</sup>R<sup>19</sup>, C(O)R<sup>20</sup>, CO<sub>2</sub>R<sup>21</sup>, NR<sup>22</sup>CO<sub>2</sub>R<sup>23</sup>, C<sub>1-6</sub> alkyl, CF<sub>3</sub>, C<sub>1-6</sub> alkoxy(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy, OCF<sub>3</sub>, C<sub>1-6</sub> alkoxy(C<sub>1-6</sub>)alkoxy, C<sub>1-6</sub> alkylthio, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-10</sub> cycloalkyl (itself optionally substituted by C<sub>1-4</sub> alkyl or oxo), methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C<sub>1-4</sub>)alkyl,

phenoxy, phenylthio, phenyl(C<sub>1-4</sub>)alkoxy, heterocyclyl, heterocyclyl(C<sub>1-4</sub>)alkyl,

heterocyclioxy or heterocyclyl(C<sub>1-4</sub>)alkoxy; wherein any of the immediately foregoing phenyl and heterocyclyl moieties are optionally substituted with halogen, hydroxy, nitro, S(O)<sub>q</sub>(C<sub>1-4</sub> alkyl), S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH(C<sub>1-4</sub> alkyl), S(O)<sub>2</sub>N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for R<sup>5</sup> and R<sup>6</sup> below), cyano, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C(O)NH<sub>2</sub>, C(O)NH(C<sub>1-4</sub> alkyl), C(O)N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for R<sup>5</sup> and R<sup>6</sup> below),

below),  $\text{CO}_2\text{H}$ ,  $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHC(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHS(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{CF}_3$  or  $\text{OCF}_3$ ;

p and q are, independently, 0, 1 or 2;

$\text{R}^3$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{10}$ ,  $\text{R}^{11}$ ,  $\text{R}^{12}$ ,  $\text{R}^{13}$ ,  $\text{R}^{14}$ ,  $\text{R}^{15}$ ,  $\text{R}^{16}$ ,  $\text{R}^{18}$ ,  $\text{R}^{19}$ ,  $\text{R}^{20}$ ,  $\text{R}^{21}$  and  $\text{R}^{22}$  are,

5 independently, hydrogen,  $\text{C}_{1-6}$  alkyl (optionally substituted by halogen, hydroxy or  $\text{C}_{3-10}$  cycloalkyl),  $\text{CH}_2(\text{C}_{2-6} \text{ alkenyl})$ , phenyl (itself optionally substituted by halogen, hydroxy, nitro,  $\text{NH}_2$ ,  $\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below),  $\text{S(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,

10  $\text{S(O)}_2\text{NH}_2$ ,  $\text{S(O)}_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below), cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{C(O)NH}_2$ ,  $\text{C(O)NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below),  $\text{CO}_2\text{H}$ ,  $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$ ,

15  $\text{NHC(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHS(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{CF}_3$  or  $\text{OCF}_3$  or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro,  $\text{NH}_2$ ,  $\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below),  $\text{S(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{NH}_2$ ,  $\text{S(O)}_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,

20  $\text{S(O)}_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below), cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{C(O)NH}_2$ ,  $\text{C(O)NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below),  $\text{CO}_2\text{H}$ ,  $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHC(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHS(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{CF}_3$  or  $\text{OCF}_3$ ;

alternatively  $\text{NR}^5\text{R}^6$ ,  $\text{NR}^7\text{R}^8$ ,  $\text{NR}^{12}\text{R}^{13}$ ,  $\text{NR}^{14}\text{R}^{15}$ ,  $\text{NR}^{18}\text{R}^{19}$ , may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, morpholine or piperazine, the latter optionally substituted by  $\text{C}_{1-4}$  alkyl on the distal

25 nitrogen;

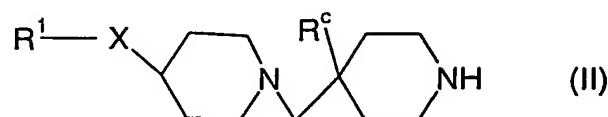
$\text{R}^4$ ,  $\text{R}^{17}$  and  $\text{R}^{23}$  are, independently,  $\text{C}_{1-6}$  alkyl (optionally substituted by halogen, hydroxy or  $\text{C}_{3-10}$  cycloalkyl),  $\text{CH}_2(\text{C}_{2-6} \text{ alkenyl})$ , phenyl (itself optionally substituted by halogen, hydroxy, nitro,  $\text{NH}_2$ ,  $\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  above),  $\text{S(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,

30  $\text{S(O)}_2\text{NH}_2$ ,  $\text{S(O)}_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  above), cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{C(O)NH}_2$ ,  $\text{C(O)NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  above),  $\text{CO}_2\text{H}$ ,  $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$ ,

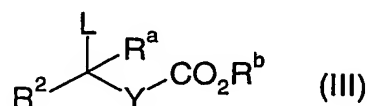
- NHC(O)(C<sub>1-4</sub> alkyl), NHS(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), C(O)(C<sub>1-4</sub> alkyl), CF<sub>3</sub> or OCF<sub>3</sub>) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH<sub>2</sub>, NH(C<sub>1-4</sub> alkyl), N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for R<sup>5</sup> and R<sup>6</sup> above), S(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH(C<sub>1-4</sub> alkyl),
- 5 S(O)<sub>2</sub>N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for R<sup>5</sup> and R<sup>6</sup> above), cyano, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C(O)NH<sub>2</sub>, C(O)NH(C<sub>1-4</sub> alkyl), C(O)N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for R<sup>5</sup> and R<sup>6</sup> above), CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub> alkyl), NHC(O)(C<sub>1-4</sub> alkyl), NHS(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), C(O)(C<sub>1-4</sub> alkyl), CF<sub>3</sub> or OCF<sub>3</sub>);
- 10 or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof.
2. A compound as claimed in claim 1 wherein R<sup>1</sup> is phenyl optionally substituted with halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy.
- 15 3. A compound as claimed in claim 1 or 2 wherein X is O.
4. A compound as claimed in claim 1, 2 or 3 wherein R<sup>a</sup> and R<sup>c</sup> are both hydrogen.
- 20 5. A compound as claimed in claim 1, 2, 3 or 4 wherein Z is CO<sub>2</sub>R<sup>b</sup>.
6. A compound as claimed in claim 1, 2, 3, 4 or 5 wherein Y is a bond or alkylene (optionally substituted by C<sub>1-4</sub> alkyl); R<sup>a</sup> is hydrogen; and, R<sup>2</sup> is hydrogen, C<sub>1-6</sub> alkyl, phenyl (optionally substituted by halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or
- 25 NHC(O)(C<sub>1-4</sub> alkyl)) or heterocyclyl (optionally substituted by halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy).
7. A compound as claimed in claim 1, 2, 3, 4 or 5 wherein Y is phenylene (optionally substituted by halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy) or heterocyclylene (optionally substituted by halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy); R<sup>a</sup> is hydrogen; and R<sup>2</sup> is
- 30 hydrogen or C<sub>1-4</sub> alkyl.

8. A process for preparing a compound of formula (I) as claimed in claim 1, the process comprising:

a) coupling a compound of formula (II):

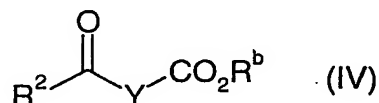


5 with a compound of formula (III):



wherein L is a suitable leaving group;

- b) when Rᵃ is hydrogen and Z is CO₂Rᵇ, reductive amination of a compound (II) with a compound of formula (IV):

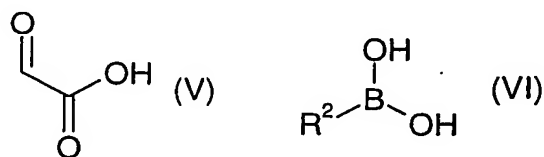


10

wherein Rᵇ is C<sub>1-4</sub> alkyl, in the presence of NaBH(OAc)<sub>3</sub> and acetic acid, or NaBH<sub>3</sub>CN in a suitable solvent, optionally followed by hydrolysis of the ester group;

15

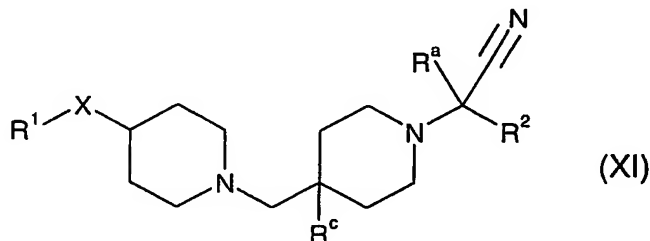
- c) when Y is a bond, Rᵃ and Rᵇ are both hydrogen and Z is CO<sub>2</sub>H, a three component coupling of a compound of formula (II) with compounds of formula (V) and (VI):



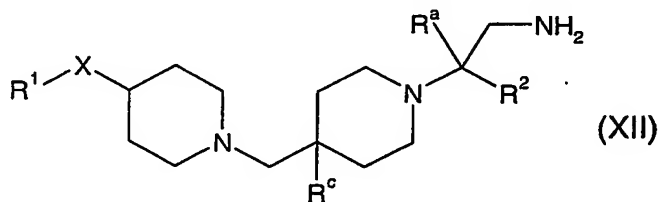
in a suitable solvent at a suitable elevated temperature;

20

- d) when Y is a bond and Z is CO<sub>2</sub>H, performing a nitrile hydrolysis on a compound of formula (XI):



- e) when Z is tetrazol-5-yl, reacting a compound of formula (XI) with  $(\text{CH}_3)_3\text{SiN}_3$  and  $(\text{Bu}_3\text{Sn})_2\text{O}$  at an elevated temperature;
- f) when Z is  $\text{NHS}(\text{O})_2\text{CF}_3$ , reacting a compound of formula (XII):



5 with triflic anhydride at a reduced temperature.

9. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.
- 10
10. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, for use in therapy.
11. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, in the manufacture of a medicament for use in therapy.
- 15
12. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1.
- 20